Nosocomial Diarrhea in the Intensive Care Unit

Ana Paula Marcon, Mônica Antar Gamba and Lucila Amaral Carneiro Vianna

Department of Nursing, Federal University of São Paulo; São Paulo, SP, Brazil

We made an epidemiological case-control study to examine risk factors for the development of diarrhea in the intensive care unit (ICU) of a public hospital in Santo André, SP, from January to October 2002. Forty-nine patients with diarrhea (cases) and 49 patients without diarrhea (controls), matched for age and gender, were included in the study. A stool culture and enzyme immunoassays for *Clostridium difficile* toxins A and B were performed on fecal specimens from diarrhea patients. Fourteen of them presented positive cultures for *Pseudomonas aeruginosa* and 22 patients presented positive ELISA for *Clostridium diffícile*. Nosocomial diarrhea was associated with several factors, including use of antibiotics (P=0.001), use of ceftriaxone (P=0.001), presence of infection (P=0.010) and length of hospital stay (P=0.0001).

Key Words: Nosocomial infections, diarrhea, antibiotics, intensive care, *Clostridium difficile*.

Nosocomial diarrhea often goes unnoticed in hospitalized patients. Even if specifically tested for, it is generally considered a consequence of an enteral diet a hospital-acquired gastrointestinal infection; other risk factors to which these patients are exposed are not even considered. Fernandes et al. [1] defined severe diarrhea as a change in the normal intestinal habit of the patient, with an increase in the frequency and/or a reduction in the consistency of the feces. McFarland [2], Fernandes et al. [1] and Bauer et al. [3] define nosocomial diarrhea as a common response to an array of harm caused by therapy, which frequently occurs in hospitalized patients, including intolerance to or overdose of medications, ingestion of hyperosmolar solutions or laxatives, diseases associated with antibiotics, therapeutic procedures, chronic disease, overeating or the acquisition of a hospital pathogen (bacteria or virus).

A literature review on nosocomial diarrheas revealed a prevalence of 8% to 21% of nosocomial diarrhea cases, increasing to 38% in the case of outbreaks [2]. In the hospital environment, patients suffer from bacterial colonization, including *Clostridium difficile*, which is one of the most frequent causes of nosocomial gastrointestinal infection [1-4]. It is currently considered the primary cause of infectious nosocomial diarrhea in developed countries [5]. Diarrhea associated with antibiotics is also a very common problem among hospitalized patients, particularly if the antibiotic acts against anaerobic bacteria [6,7].

Our objective was to identify factors associated with diarrhea acquired in an intensive care unit and relate them to clinical variables, including diagnosis, hospitalization and treatment.

Received on 11 June 2006; revised 17 October 2006.
Address for correspondence: Dr. Ana Paula Marcon. Rua Paulo Novais, 1082 - Vila Vitória, Santo André, São Paulo, Brazil
Zip code: 09172-420. E-mail: paula_carniel@yahoo.com.br

The Brazilian Journal of Infectious Diseases 2006;10(6):384-389.

Material and Methods

We made an epidemiological case-control study in the intensive care unit of a public hospital in Santo André, SP; 49 cases and 49 controls were included.

Definition of case

The following criteria were used in selecting the cases: patients who had been in the ICU for more than 72 hours, patients who presented three or more episodes of liquid evacuation in 24 hours [8], and patients who were free of gastrointestinal diseases and who were not immunocompromised. The inclusion criterion of being in the ICU for more than 72 hours was included to reduce the chance of diarrhea from factors outside the ICU [1,3,9]. According to McFarland [2], immunocompromised patients, who include carriers of the human immunodeficiency virus (HIV), generally suffer from infectious diarrhea of non-bacterial and non-hospital etiology, due to viruses, protozoans and fungi. This is why they were excluded from the study.

Definition of control

Patients were included who at the time of data collection presented no diarrhea. To reduce the differences between the groups, the cases were age and gender matched to the controls. Matching was 1:1; a control was matched to each case of the same gender who was no more than four years older or younger and who had been hospitalized for more than 72 hours, in the same ICU, for the same data collection period as the cases (from January to October, 2002).

Data collection

After approval by the UNIFESP Ethics Committee and the hospital administration, the ICU nursing team was informed of the topic and of the importance of the study; information

was then requested in person or by telephone concerning any episodes of diarrhea in ICU patients, in addition to daily review of nursing notations by the first author. A published definition for diarrheic feces was used: "feces that take the shape of the recipient in which they are placed…" [3]. This definition became necessary because each professional has a different idea of what diarrheic feces are.

Authorization from the patient or family was requested for inclusion in the study; with their consent the researcher filled out a questionnaire for each of the patients. In addition to the questionnaire, feces were gathered from the patients with diarrhea (cases) in two recipients: one for a stool culture and the other for an enzyme immunoassay (RIDASCREEN® *Clostridium diffícile* Toxin A/B Kit) to check for toxins A and B, as described by McFarland et al. [9].

Clinical variables

The following variables were chosen because they had already been cited by other authors as risk factors for nosocomial diarrhea: an enteral diet, length of stay in the ICU, systemic antibiotic therapy, antibiotic type, presence and locale of infection (hospital or non-hospital setting), diagnosis, presence of roommates with diarrhea in the ICU and use of laxatives; the latter two variables were not controlled, and feces collection for stool culture and the test for *Clostridium diffícile* toxins were conducted only for the cases.

A descriptive analysis of the data was performed by creating simple frequency distributions and contingency tables. The statistical analyses were performed with the STATACORP 1995 program. McNemar chi-square and odds Ratio (OR), with their respective confidence intervals, were estimated for the controlled variables. A significance level (α) of 0.05 (α= 5%) was adopted.

Results

During the data collection period, 342 patients were observed, of which 54 presented nosocomial diarrhea; five of these were not included in our study due to a lack of feces sample collection. The mean age of patients with nosocomial diarrhea was 53.9 years, and the median was 54 years. The youngest patient among both the cases and controls was 13 years old, and the oldest in both groups was 94 years old; 55% (27) were men and 45% (22) women.

Among the 54 patients with diarrhea, five used laxatives; which were given as a glycerol solution enema – FLEET ENEMA® (Table 1). The presence of roommates with diarrhea was observed on the day each patient was included in the study: 86% (42) of the patients had roommates with diarrhea in the ICU. Twenty-nine percent of 49 patients (n = 14) had positive stool cultures. *Pseudomonas aeruginosa* was found in all of these samples. In the test for *Clostridium difficile* in the feces, a positive result indicated that toxins A and B were found, or both simultaneously (Table 1). The tests with indeterminate results indicated that the samples were not clearly negative or positive and would require fresh feces samples for retesting [10], which was not possible, since the samples were collected during 10 months and were frozen immediately after collection. The tests for toxins were all performed at the end of the collection period.

Table 1. Distribution of patients with diarrhea (cases) according to clinical variables, in a public hospital in Santo André, SP, 2002

Clinical variables	N (total = 49)	%
Use of laxatives		
Yes	5	10.2
No	44	89.8
Roommate with diarrhea		
None	7	14.3
One or more	42	85.7
Stool culture		
Positive	14	28.6
Negative	35	71.4
Test for *Clostridium difficile*		
Positive	22	44.9
Negative	17	34.7
Indeterminate	10	20.4

Analysis of cases and controls — McNemar chi-square and odds ratio

The variable use of enteral diet was not significantly associated with nosocomial diarrhea (Table 2, P = 0.424). The case group had a higher frequency of use of antibiotics (odds ratio (OR) = 13.0, 95% confidence interval (CI) = 1.95 – 552.38) and P=0.001. We also found infection (hospital or non-hospital acquired) to be a factor associated with nosocomial diarrhea, with OR = 3.6 (95% CI 1.29 – 12.40) and P=0.01. The locale of infection for the patients was not significantly associated with the occurrence of diarrhea. Among the cases 51% (25) and 22% (11) of the controls were treated with ceftriaxone (Table 2). There was a positive association between the use of this drug and diarrhea, with OR = 8.0 (95% CI = 1.88 – 71.71) and P=0.001. None of the other antibiotics were associated with nosocomial diarrhea.

Pneumopathy, at 41% (20), involving mainly hospital, and community-acquired pneumonias, was the most common diagnosis among patients with diarrhea (Table 3), while the most common diagnoses among the controls was cardiopathy (34.7%) and post-operative neurosurgery and pneumopathy (24.5% of the controls, in each). Despite these high frequencies, no significant association was found between the variable diagnosis and nosocomial diarrhea.

Table 2. Distribution of diarrhea cases and controls according to clinical variables, in a public hospital in Santo André, SP, 2002

Variables	Cases (%) (n=49)	Controls (%) (n=49)	OR	CI (95%)	P
Use of enteral diet	61.2	51.0	1.5	0.63 – 3.73	0.424
Use of antibiotics	95.9	69.5	13.0	1.95 – 552.38	0.001
Type of antibiotic*					
Imipenem	16.3	10.2	2.0	0.43 – 12.36	0.507
Ceftriaxone	51.0	22.4	8.0	1.88 – 71.71	0.001
Clindamycin	24.5	8.2	3.0	0.91 – 12.76	0.077
Amicacin	44.9	28.6	1.8	0.79 – 4.36	0.184
Vancomycin	16.3	16.3	1.0	0.29 – 3.34	>0.999
Presence of infection**	69.4	42.8	3.6	1.29 – 12.40	0.010
Site of infection					
Respiratory	36.7	18.4	2.5	0.92 – 7.86	0.078
Urinary tract	16.3	12.2	1.7	0.32 – 10.73	0.727
Bloodstream	20.4	14.3	1.5	0.48 – 5.12	0.607

*Various patients used more than one antibiotic. **Hospital and nonhospital infections, except for gastrointestinal.

Table 3. Distribution of diarrhea cases and controls according to diagnosis*, in a public hospital in Santo André, SP, 2002

Diagnosis	Cases (%) (n=49)	Controls (%) (n=49)	OR	CI (95%)	P
Cardiopathy	18.4	34.7	0.33	0.78 – 1.10	0.070
Pneumopathy	40.8	24.5	2.14	0.82 – 6.21	0.134
Nephropathy	24.5	12.2	2.50	0.72 – 10.92	0.180
Contagious disease	8.2	2.0	4.00	0.39 – 196.99	0.375
Polytrauma	8.2	4.1	3.00	0.24 – 157.49	0.625
Hepatopathy	2.0	—	***	***	>0.999
Neuropathy**	26.5	12.2	3.33	0.86 – 18.85	0.09
Malignant neoplasia	2.0	4.1	0.50	0.008 – 9.60	>0.999
Post operative neurosurgery	10.2	24.5	0.30	0.53 – 1.16	0.092
Post operative gastrointestinal surgery	16.3	16.3	1.00	0.27 – 3.74	>0.999
Hypertension	24.5	14.3	2.00	0.62 – 7.46	0.302
Diabetes mellitus	14.3	6.1	5.00	0.56 – 236.45	0.218
Coagulopathy	8.2	—	***	***	0.125
Gunshot wound	2.0	—	***	***	>0.999

*Various patients had more than one diagnosis;** Neuropathy non-surgical;***OR not estimable.

The length of hospital stay was significantly affected; the cases were hospitalized for a mean of 17 (95% CI = 9 – 25) days more than the controls (P =0.0001).

A conditional logistical regression was carried out as a part of the multivariate analysis, using variables that gave P < 0.10 in the univariate analysis. The variables use of antibiotics, use of ceftriaxone and use of clindamycin were not evaluated because the sample did not have enough pairs in each of these categories, which led to confidence intervals with excessively high amplitude. The variables presence of infection, cardiopathy, presence of infection, pneumonia, and clinical neuropathy were analyzed together and were found not to be significantly associated with nosocomial diarrhea. However, length of hospital stay was significantly associated, with OR = 1.09 (95% CI = 1.032 – 1.165).

Discussion

Nosocomial diarrhea occurs frequently in patients receiving intensive care; it becomes a serious problem because patients are generally exposed to various factors that tend to reduce their immunity and aggravate the diarrhea [3]. Patients who acquire nosocomial diarrhea are hospitalized for longer periods of time, become exposed to other hospital infections, and they have a higher mortality rate than patients without diarrhea; there is also a high risk of transmission to other patients [2,11]. The length of hospital stay increases an average

of eight days with the acquisition of nosocomial diarrhea [2]. Elderly patients were found to be even more affected, with an average increase of 36 days of hospitalization due to nosocomial diarrhea [12].

Diarrhea associated with *Clostridium difficile,* which we also investigated in our study, is of considerable importance due to the burden it places on individuals, health services and the government. A prospective cohort study, carried out by Kyne et al. [5], evaluated 47 patients with diarrhea associated with *Clostridium difficile* and found an average expenditure of US$10,489 per hospital stay, which is US$ 3,669 (95% CI = 1,126 – US$ 7,024) more than the cost of a hospital stay for patients without diseases associated with *Clostridium difficile*.

The mean age of our patients with diarrhea was 53.9 years (95% CI = 48.0 – 59.9), with a median age of 54 years. Age is known to be an important risk factor; McFarland [2] reported an incidence of nosocomial diarrhea in adults of from 3 to 28 for every 100 admissions, while in elderly patients (over 70 years) it was 17 to 31 for every 100 admissions. He also conducted a cohort study and calculated a relative risk of 6.6, 11.8 and 14.3 for the age groups 41 to 60, 61 to 75 and over 75 years, respectively [9].

Among the infectious causes of nosocomial diarrhea, *Clostridium difficile* is the most important from an epidemiological standpoint. According to Bauer et al. [3], hospitalized patients with diarrhea who have been or who are being treated with antibiotics and cytostatics should always have their feces tested for *Clostridium difficile*. Kuijper et al. [13] reported that diarrhea caused by *Clostridium difficile* occurs more frequently in elderly patients who have been submitted to surgery and in patients placed in the ICU. In another study, carried out in England, 75% of the cases of intestinal infection caused by *Clostridium difficile* occurred in patients over 64 years of age [5]. In a study conducted with 399 patients, the relative risk of acquiring nosocomial diarrhea associated with *Clostridium difficile* was 5.8 for patients aged 41 to 60 and 9.6 for patients aged 61 to 75 [1]. In our study, the mean age of patients with positive ELISA for *Clostridium difficile* was 48.7 years, with a median age of 48. Winström et al. [7] found no significant association between the occurrence of diarrhea and age; they stated that many studies have overestimated this association because they were carried out in hospital settings with predominantly elderly populations.

Only 10.2% (5) of the cases in our study used enemas and none of them used orally-administered laxatives (Table 1). Bauer et al. [3] cite laxative agents as one of the main iatrogenic causes of nosocomial diarrhea. McFarlandet al. [9] found a relative risk of 2.96 (95% CI=1.36 – 10.20) for diarrhea after enemas.

There were one or more roommates in the ICU with diarrhea on the day that each case was elected for our study in 86% (42) of the cases. According to McFarland [1], the relative risk for acquisition of *Clostridium difficile* by a non-colonized patient increases significantly if he is hospitalized in a room with a patient colonized or infected by this bacterium, with a relative risk of 1.73 (95% CI = 1.15 – 2.55). Similarly, Kyne et al. [5] cite a study in which it was proven that patients who shared a room with a patient colonized with *Clostridium difficile* would acquire it more rapidly (after a mean of 3.2 days) than patients hospitalized in private rooms or with roommates who had tested negative for *Clostridium difficile* (18.9 days).

The patients with diarrhea presented 14 stool cultures positive for *Pseudomonas aeruginosa*. This bacterium has been found as part of the resident flora of the intestinal tract in some humans without causing infection [14,15]. Kim et al. [16], in a study conducted in South Korea on seven patients, found an association between antibiotics used in diarrhea caused by strains of *Pseudomonas aeruginosa* resistant to same antibiotics that had been previously used by the patients, which suggests that *Pseudomonas aeruginosa* is a cause of diarrhea associated with the use of antibiotics; among the seven patients, one tested positive for *Clostridium difficille* toxins. In our study, of the 14 patients with a stool culture positive for *Pseudomonas aeruginosa*, six also had positive ELISA for *Clostridium difficile*.

The enzyme immunoassay for the detection of *Clostridium difficile* toxins A and B detected 45% (22) positive, 35% (14) negative and 20% (10) indeterminate results. *Clostridium difficile* is generally resistant to penicillins and cephalosporins, while most anaerobic bacteria of the intestinal flora are susceptible. So, administration of these drugs provides excellent conditions for overgrowth of *Clostridium difficile* [9]. Many different antibiotics have been associated with nosocomial diarrhea; antibiotics whose spectrum of activity includes anaerobic bacteria, mainly cephalosporins, penicillins, clindamycin and vancomycin, are the most frequently associated [1,3,9,17]. Safdar and Maki [18] also stated that broad-spectrum antibiotics are a major cause of diarrhea associated with antibiotics and colitis caused by *Clostridium difficile.*

Bartlett [17] defines diarrhea associated with antibiotics (DAA) as a diarrhea of unknown etiology that occurs in patients who are using antibiotics; in 10% to 20% of these DAA cases, *Clostridium difficile* infection is found. The physiopathological explanation for DAA is that antibiotics reduce the concentration of anaerobic bacteria normally present in the intestine; this can decrease carbohydrates metabolism and cause osmotic diarrhea. We found a significant association between the use of antibiotics in general and the occurrence of diarrhea, with OR = 13.0 (95% CI = 1.95 – 552.38) and P = 0.001. These data point to a need for studies with larger sample sizea. When the antibiotics were analyzed separately, a positive association was found between nosocomial diarrhea and the use of ceftriaxone, with OR = 8.0 (95% CI = 1.88 – 71.71) and P =0.001; McFarland [1] also reported that 40% of patients who were treated with

cephalosporins developed nosocomial diarrhea. Use of third-generation cephalosporins was also found to be significantly (P =0.02) associated with nosocomial diarrhea by Schwaber et al. [11]. They also found a significant association between *Clostridium difficile* and use of third-generation cephalosporins (P = 0.02). The number of antibiotics that the patient uses also influences the occurrence of diarrhea associated with *Clostridium diffícile.* In our study, 57% (28) of the cases were treated with more than one antibiotic, and among the 22 patients who tested positive for *Clostridium difficile*, 64% (14) had used two or more antibiotics. McFarland et al. [9] detected *Clostridium difficile* in 83 patients, among which 17% (14) had had used only one antibiotic and 65% (54) had used multiple antibiotics. Schwaber et al. [11] also found an association between the use of various antibiotics and the occurrence of nosocomial diarrhea (P = 0.02).

In our present study, the variable use of enteral diet showed no association with diarrhea, with OR= 1.5 (95% CI= 0.63 – 3.73) and P =0.424; unlike the study of Zaidi et al. [19], who examined various risk factors for nosocomial diarrhea and, among others, found an OR = 67 for patients on an enteral diet. Another study considered the presence of an enteral probe as a risk factor, with a relative risk of 3.8 (95% CI=1.88 – 7.51) [3]. In their study, Safdar and Maki [18] found a relative risk of 1.4 to 19.7 for patients using an enteral feeding tube. Bliss et al. [20] reported that diarrhea is a frequent complication in patients using a feeding tube.

Okuma [21] found bacterial contamination in ready-made enteral diets; they examined 49 empty, unused bottles and found one contaminated unit. He did not report which microorganisms were found in the bottle. The enteral diets were not analyzed because they are ready for use, are administered in a closed system and present only a slight chance of contamination.

Infection, regardless of the site where it is found, is a risk factor for nosocomial diarrhea. A relative risk of 3.44 (95% CI =1.79 – 6.63) for diarrhea has been reported for patients who suffer from other hospital infections [9]. A greater occurrence of diarrhea was found in patients with infections (hospital or non-hospital), regardless of site (P = 0.010) in both this and our studies. When we examined specific sites, neither the respiratory system, urinary tract or the bloodstream were significantly associated with diarrhea (Table 2).

We found no association between the diagnosis and nosocomial diarrhea (Table 3), although some chronic diseases have been found to be associated with nosocomial diarrhea, including pancreatic islet cell tumors, carcinomas, hypoparathyroidism, neuropathy, diabetes, gastrointestinal cancer, uremia, lesions or masses of the colon, and endocrinological diseases [1,3]. In our study, three patients (6%) had malignant neoplasias and 10 (20%) had diabetes.

We compared the mean length of hospital stay of the cases (26.8 days) and controls (10.12 days). A difference of 17 additional days of hospitalization for the cases was found (P =0.0001). Various studies have also reported length of hospital stay as a conditioning factor for the occurrence of nosocomial diarrhea. A study conducted in 1989 by McFarland et al [22]. with adult patients reported a mean length of hospital stay of 11.3 days for patients who did not acquire diarrhea and 19.8 days for patients who developed nosocomial diarrhea. Guyot and Barret [23] found that a hospital stay longer than 28 days was a risk factor for diarrhea associated with *Clostridium difficile*. A cohort study carried out in Seattle suggests that a hospital stay of more than four days increases the relative risk for nosocomial diarrhea; patients hospitalized for eight to 14 days had a relative risk of 2.71 (95% CI = 0.41 – 17.91) for the acquisition of diarrhea by *Clostridium difficile*, while patients hospitalized for 15 to 114 days had a relative risk of 5.09 (95% CI=1.12 – 23.15) [9].

Conclusions and Considerations

Our objective was to study diarrhea acquired in the ICU. The main factors associated with nosocomial diarrhea were: the use of antibiotics in general, use of cefriaxone in particular, infection (hospital or non-hospital acquired) and length of hospital stay in the ICU.

We conclude that there is a need for further investigation on the acquisition of diarrhea in the ICU. The presence of *Pseudomonas aeruginosa* in feces is something that should be investigated; such a study would ideally include the creation of an antimicrobial sensitivity profile to identify community and hospital strains. Before our study, the possibility of diarrhea associated with *Clostridium difficile* had not been considered. Now armed with this knowledge, professionals will be aware of the problem and will prescribe broad-spectrum antibiotics only when there is a real need for them. The finding of *Pseudomonas aeruginosa* and *Clostridium difficile* in feces, combined with the fact that 86% of the patients with diarrhea had one or more roommates with diarrhea in the ICU, alerts us to the importance of hand washing before and after procedures, as well as a need for adoption of universal precautions for all patients and for precautionary measures for contact with patients with diarrhea.

References

1. Fernandes A.T., et al. Infecção Hospitalar e suas interfaces na área da saúde. Ateneu, São Paulo: **2000**.
2. Mcfarland L.V. Diarrhea acquired in the hospital. Gastroenterol Clin North America **1993**;22(3):563-77.
3. Bauer T.M., Kist M., Daschner F., Blum H.E. Nosokomiale diarrhoe. Dtsch Med Wochenschr **2001**;126:1431- 4.
4. Suyletir G., et al. *Clostridium difficile* acquisition rate and role in nosocomial diarrhoea at a university hospital in Turkey. Eur J Epidemiol **1996**;12(4):391-4.
5. Kyne L., Farrel R.J., Kelly C.P. *Clostridium difficile*. Gastroenterol Clin North America **2001**;30(3):753- 75.

6. Bliss D.Z., Guenter P.A., Settle R.G. Defining and reporting diarrhea in tube-fed patients-what a mess! Am J Clin Nutr, v.55, p.753- 759, 1992 apud McFarland L.V. Diarrhea acquired in the hospital. Gastroenterol Clin North America **1993**;22(3):563-77.
7. Winström J., et al. Frequency of antibiotic-associated diarrhoea in 2462 antibiotic-treated hospitalized patients: a prospective study. J Antimicrob Chemother **2001**;47:43-50.
8. World Health Organization. The treatment and prevention of acute diarrhoea: pratical guidelines. Geneva, **1989**.
9. Mcfarland L.V., Surawicz C.M., Stamm W.E. Risk factors for Clostridium difficile carriage and *Clostridium difficile* – associated diarrhea in a cohort of hospitalized patients. J Infect Dis **1990**;162:678-84.
10. R-biopharm. Ridascree N. *Clostridium difficile* Toxin A/ B. Art. Nº C0801. Germany, **2001**.
11. Schwaber M.J., et al. Factors associated with nosocomial diarrhea and *Clostridium difficile* associated disease on the adult wards of an urban tertiary care hospital. Eur J Clin Microbiol Infect Dis **2000**;19(1):9-15.
12. Eriksson S., Aronsson B. Medical implication of nosocomial infection with *Clostridium difficile*. Scan J Infect Dis **1989**;21:733-4.
13. Kuijper E.J., et al. Nosocomial outbreak of *Clostridium difficile*-associated diarrhoea due to a clindamycin-resistant enterotoxin A- negative strain. Eur J Clin Microbiol Infect Dis **2001**;20:528-38.
14. Wenzel R.P. Prevention and control of nosocomial infection. 3 ed. Williams & Wilkins, Baltimore: **1997**.
15. Martins S.T. Análise de custos da internação de pacientes em unidade de terapia intensiva com infecções causadas por *Pseudomonas aeruginosa* e *Acinetobacter baumannii* multirresistentes. São Paulo, **2002**. M.Sc. thesis, Universidade Federal de São Paulo.
16. Kim S.W., et al. *Pseudomonas aeruginosa* as a potential cause of antibiotic-associated diarrhea. J Korean Med Sci **2001**;16(6):742-4.
17. Bartlett J.G. Antibiotic-associated diarrhea. N Engl J Med **2002**;346(5):334-49.
18. Safdar N., Maki D.G. The commonality of risk factors for nosocomial colonization and infection with antimicrobial-resistant *S. aureus*, Enterococcus, Gram-negative bacilli, *Clostridium difficile* and Candida. Ann Intern Med **2002**;136(11):834-41.
19. Zaidi M., et al. Hospital-acquired diarrhea in adults: a prospective case-controlled study in México. Infect Control Hosp Epidemiol **1991**;12:349-55.
20. Bliss D.Z., et al. Fecal incontinence in hospitalized patients who are acutely ill. Nurs Res **2000**;49(2):101-7.
21. Okuma T., et al. Microbial contamination of enteral feeding formulas and diarrhea. Nutrition **2000**;16(9):719-22.
22. Mcfarland L.V., et al. Nosocomial acquisition of *Clostridium difficile* infection. N Engl J Med **1989**;320:204-10. Apud McFarland L.V. Diarrhea acquired in the hospital. Gastroenterol Clin North America **1993**;22(3):563-77.
23. Guyot A., Barret S.P. What is an appropriate control group to identify risk factor for *Clostridium difficile* associated diarrhoea [letter]. J Antimicrob Chemother **2001**;48:747-8.